ABSTRACT

Encouragement of Young Investigator Award Lectures

AL1 Dentate neural circuit formation in disease

Ryuta Koyama

Lab. Chem. Pharmacol., Grad. Sch. Pharmaceut. Sci., Univ. Tokyo

Precise neural circuit formation during development is fundamental for proper brain function in adulthood. We have investigated the cellular and molecular links between prenatal stress and adult depressive disorders and between postnatal seizures and adult epilepsy. First, using a rat model of prenatal stress, we found that prenatal stress impairs the morphological and functional maturation of dentate granule cell dendrites in adult offspring via the down-regulated expression of mineralocorticoid receptors. Second, using a rat model of complex febrile seizures, we found that postnatal febrile seizures attenuate the proper migration of dentate granule cells, which result in the emergence of ectopic granule cells in adulthood, via increased excitatory $GABA_A$-receptor signaling. Thus, our study would contribute to discover novel therapeutic targets for early-life events-induced brain diseases.

AL2 Pharmacological studies on the pathophysiological roles of cation channels in the activation of glial cells

Hisashi Shirakawa

Dept. Mol. Pharmacol., Grad. Sch. Pharm. Sci., Kyoto Univ.

Abnormal activation of glial cells is the key feature in neuroinflammation which contributes to disturb the brain function. Here we focus on the cation channels, especially transient receptor potential (TRP) superfamily, which could be involved in the pathogenesis of the CNS diseases. TRP superfamily comprises a group of Ca^{2+}-permeable non-selective cation channels that open in response to divergent stimuli in their environment. Although TRP channels are widely distributed in the mammalian brain, their pathophysiological roles in the glial cells remain to be elucidated. In vitro and in vivo experiments demonstrate that 1) TRPC3 contributes to the pathological activation of astrocytes through a feed-forward upregulation of its own expression and TRPC3 inhibitor Pyr3 improves outcomes and attenuates astrogliosis after intracerebral hemorrhage in mice, 2) the opening of TRPV4 channel attenuates the driving force for extracellular Ca^{2+} and suppresses microglial activation, 3) TRPM2-mediated Ca^{2+} signaling increases nitric oxide production in microglia and could be involved in cerebral ischemic injury. These results suggest that the above-mentioned TRP channels may constitute a new therapeutic target for CNS disorders.

AL3 Discovery of anti-inflammatory role of prostaglandin D_2

Takahisa Murata

Dept. Animal Radiology, Tokyo Univ.

Inflammation is a protective tissue response to infection, injury or tissue destruction. Insufficient inflammation aggravates infection and delays tissue healing while excessive and/or sustained inflammation results in various diseases, and in some cases it leads tumorigenesis. Thus detail study investigating how inflammation is regulated by both pro- and anti-inflammatory signaling is necessary to treat the inflammatory diseases.

Cyclooxygenases (COX) and its metabolites, the prostaglandins (PGs), are critical during an inflammatory response. Major PGs such as PGE_2, $PGF_2\alpha$, PGI_2 and Thromboxane A_2 has been well-recognized as pro-inflammatory mediators. In our studies using mouse experimental models, we found that another PG, PGD_2 act as an anti-inflammatory mediator in lung inflammation, skin inflammation, colitis and tumor and that its signal enhancement treats these diseases. Our findings implicate the therapeutic potential of PGD2 signal in a variety of inflammatory diseases.

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